Scientific Abstract for Clinical Protocol AAV-hAADC-2-003

Primary Investigator: Michael J. Aminoff, MD, DSc
Corporate Sponsor: Avigen, Inc.

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, with an estimated incidence of 1-2/1000 in the general population and 2/100 among people older than 65 years. PD results from loss of dopaminergic neurons in the substantia nigra. Its cardinal clinical features are bradykinesia, resting tremor, rigidity and postural instability, and its cardinal pathological features are the formation of large, ubiquitin-positive and synuclein-positive inclusions in the substantia nigra (and elsewhere) and loss of dopaminergic neurons. Parkinson's disease is a candidate for gene transfer because resulting underlying disturbances to the neural circuitry are well defined, there is considerable experience in pharmacological therapy for the disease, and the defect is a focal one.

The vector chosen to deliver the gene is derived from adeno-associated virus (AAV), a nonpathogenic single-stranded DNA virus that requires helper adenovirus for replication. AAV-hAADC employs AAV as a delivery vehicle for the normal human AADC gene.

Standard therapy is primarily symptomatic and pharmacologic. Levodopa, the biosynthetic precursor of dopamine, is the most common and most effective pharmacologic therapy. Levodopa crosses the blood brain barrier and is converted by the enzyme aromatic L-amino acid decarboxylase (AADC) to dopamine. With disease progression, levels of this enzyme decline and levodopa is less efficiently converted into dopamine. Progressively larger doses of levodopa/carbidopa are required for clinical response, but dose escalations eventually become limited by the development of dyskinesias (80% incidence after 5 years) and both psychotic and autonomic symptoms. Patients with advanced Parkinson's disease have limited treatment options, the most significant being implantation of a deep brain stimulating device to alleviate some symptoms.

The study proposed is a phase 1 dose escalation study to assess safety of an adeno-associated vector (AAV) based gene transfer material containing a normal human enzyme aromatic L-amino acid decarboxylase (AADC). The primary objective is to determine the safety and tolerability of intrastriatal administration of AAV-hAADC-2 in subjects with advanced Parkinson's disease. Secondary objectives include determination of the dose of AAV-hAADC-2 that most effectively restores normal levels of nigro-striatal AADC activity as determined by PET scan and to assess the effects of AAV-hAADC-2 on patient CRS (clinical rating scales) and levodopa intake.

The strategy proposed in this study involves infusion of the normal human gene for AADC into the striatum, with the rationale that increasing the levels of AADC will enhance the clinical effectiveness of administered levodopa, reducing dose requirements and thus the long-term adverse effects associated with escalating levodopa therapy.